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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,010	10/25/2001	Jonathan W. Nyce	EPI-00312	5176

21971 7590 03/02/2006

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,010	NYCE, JONATHAN W.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *160-162,165 and 187-190* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *160-162,165 and 187-190* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed December 1, 2005 have been entered. Claims 160-162, 165, 187-190 are pending.

The outstanding objection to the specification is withdrawn in view of the amendments filed December 1, 2005.

The outstanding rejection under 35 USC 102(b) is withdrawn in view of the amendments filed December 1, 2005 as the claims are recite a different particle size.

The outstanding double patenting rejection is withdrawn in view of the terminal disclaimer filed December 1, 2005.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 160-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast (4,956,355 of record) in view of Lieberman et al. (Pharmaceutical Dosage Forms, page 110, of record) and "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, page 1505 (PTO-892).

Prendergast discloses that particular dehydroepiandrosterones (DHEA) herein are useful in a pharmaceutical composition or a pharmaceutical formulation of enteral,

parental, injectable, topical, inhalations or nasal inhalation administration (see col.5 lines 32-64, 49 and 63-64). See abstract, col.1 lines 36-57, col. 4-5 and claim 6. Prendergast also discloses the effective amounts of dehydroepiandrosterones in the composition and other agents and pharmaceutically acceptable excipients within the instant claim in the compositions therein (col.5).

Prendergast does not expressly disclose the particular ranges of particle size herein, about 1.0-5 μm in size.

However, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, teaches that the optimum particle size for preparation into the pulmonary cavity is of the order of ½ to 7 μm (see page 1505).

"Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5-0.7 μm into the pulmonary cavity (see page 735 the right column).

The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Lieberman et al. teaches that a skilled artisan in pharmaceutical science would clearly knowledge that the granulation, determination of size, or size reduction of a solid pharmaceutical formulation, e.g., in nasal inhalation formulation, have several benefits, for example, as taught in a text book "Pharmaceutical Dosage Forms" Tables, (Volume

2) Ed. by Herbert A. Lieberman, Leon Leachman, and Joseph B. Schwartz (1989) at page 110.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation, since particular dehydroepiandrosterone sulfate (DHEA-S) herein are known to be in a pharmaceutical composition for inhalations or nasal inhalation administration based on Prendergast.

As discussed above, the optimum size for inhalations is known to be 0.5-0.7 μm, ½ to 7 μm into the pulmonary cavity according to "Remington: The Science and Practice of Pharmacy", and the fine particle size for inhalations is known to range 0.5-5 μm according to "Pharmaceutical Dosage Forms and Drug Delivery System". Thus, the dehydroepiandrosterone sulfate compositions of Prendergast for inhalations or nasal inhalation intrinsically comprise dehydroepiandrosterone sulphate particles having about 1-5 μm in size.

Moreover, the known teachings of these books clearly support the examiner's position that it is obvious to one of ordinary skill in the art that using conventional techniques to make inhalable, respirable or nasal formulation of the known active agents are considered well within the skill of artisan in pharmaceutical science, involving

merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 187-189 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast, Lieberman et al. and Remington as applied to claims 160-162, 165 above, and further in view of Kelly and Hill, Chapter 24: Asthma in Pharmacotherapy – A Pathophysiologic Approach, 2nd ed., 1992, pages 408-449 by Elsevier.

Prendergast, Lieberman et al. and Remington teach the composition of DHEA-S in the particle size as about 1-5 μm.

The references do not expressly teach the particle size of DHEA-S as 15-500μm.

Kelly and Hill teaches the devices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35μm in diameter (See page 432, col. 2, least two paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to formulate the particle size of the DHEA-S composition into 15-500μm.

One of ordinary skill in the art would have been motivated to formulate the particle size of the DHEA-S composition into 15-500μm. It is known that particle size of

0.5-35μm in diameter as useful in delivering drug particles into the lung. Therefore, formulating DHEA-S composition into particle size to 35μm, for example, would be reasonably expected to be useful.

Claims 160-162, 165 and 187-190 are rejected under 35 U.S.C. 103(a) as being unpatentable Nyce (5,527,789, of record) in view of Lieberman et al.,"Remington: The Science and Practice of Pharmacy", and Kelly and Hill.

Nyce discloses a pharmaceutical composition comprising the instant DHEA having the chemical formula (I) in a therapeutically effective amounts and the instant ubiquinone having the chemical formula (II) with n being from 1 to 12, 1 to 10, 6 to 10, or 10, in the therapeutically effective amounts, and a pharmaceutical carrier or diluent (see abstract, claims 13-19). Nyce also discloses the particular effective amounts of DHEA, i.e., 1-3600 mg/kg, 5-1800 mg/kg, or 20-100 mg/kg (see col.6 lines 6-7); and the particular effective amounts of ubiquinone, i.e., 1-1200 mg/kg, 30-600 mg/kg, or 50-150 mg/kg (see col.5 lines 64-66), within the instant claimed range, about 0.1-49% or about 1-20% w/w, since converting the known actual amount by actual weight to weight percentage in a composition, w/w, is considered well within conventional skills in pharmaceutical science, involving merely routine skill in the art. The pharmaceutical composition of Nyce further comprises a preservative, an antioxidant, a flavoring agent (e.g., sugar, see col.7 line 10), a buffering agent, a dispersant, or a surfactant (see col.6 line 67 to col.8 line 1, and col.7 lines 33-38) an inert base, glycerol (glycerin, see col.7 line 11-12). Nyce also discloses the instant forms of the formulation, e.g., nasal spay

(see col.7 line 17) oral, rectal, topical, transdermal, nasal, or parenteral including injectable (see col.5 lines 37-41, col.6 lines 40-67), in a solution (an aqueous liquor), suspension.

The cited prior art does not expressly disclose the particular particles of the active agents having size herein, about 1-5 μm or about 15-500 μm in size.

However, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, teaches that the optimum particle size for preparation into the pulmonary cavity is of the order of ½ to 7 μm (see page 1505).

"Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5-0.7 μm into the pulmonary cavity (see page 735 the right column).

The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Lieberman et al. teaches that a skilled artisan in pharmaceutical science would clearly knowledge that the granulation, determination of size, or size reduction of a solid pharmaceutical formulation, e.g., in nasal inhalation formulation, have several benefits, for example, as taught in a text book "Pharmaceutical Dosage Forms" Tables, (Volume 2) Ed. by Herbert A. Lieberman, Leon Leachman, and Joseph B. Schwartz (1989) at page 110.

Moreover, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5-0.7 μm or ½ to 7 μm into the pulmonary cavity (see page 735 the right column). The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Furthermore, Kelly and Hill teaches the devices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35μm in diameter (See page 432, col. 2, least two paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine and granulate the dehydroepiandrosterones particles in range of size herein for nasal inhalation, since the nasal formulation or composition comprising two instant active agents is known based on Nyce. According to conventional techniques to make inhalable, respirable or nasal formulation of the known active agents are considered well within the skill of artisan in pharmaceutical science, involving merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

The known teachings of these books clearly support the examiner's position that it is obvious to one of ordinary skill in the art that using conventional techniques to make inhalable, respirable or nasal formulation of the known active agents are considered well within the skill of artisan in pharmaceutical science, involving merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant is further requested to note that it is well settled that "intended use" of a composition or product, will not further limit claims drawn to a composition or product. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Response to Arguments

Applicant's arguments filed December 1, 2005 averring inhalation therapy as not common at the time of filing have been fully considered but they are not persuasive. It is clear from the teachings of Kelly and Hill that inhaled glucocorticoid therapy is not only well-known, but is commonly employed at the time of around 1992.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Examiner notes that Kelly and Hill, a well-known text-book reference that one of ordinary skill in the art would be charged to have possession, discloses that the particle size of aerosol composition for drug deposition is from 0.5-35μm, which is within the particle size envisioned herein. Absent showing criticality of the herein claimed particle size, one of ordinary skill in the art would be reasonably expected to optimize the particle size for optimal delivery of the DHEA or DHEA-S composition.

Applicant's arguments filed December 1, 2005 averring the present of unexpected benefits through declaration of Dr. Robinson have been considered, but are not found persuasive. The alleged unexpected benefit is probably well known especially taught in Kelly and Hill in page 431, col. 1, third paragraph. It teaches that the inhaled glucocorticoids produce does-dependent suppression of the adrenal cortex, but much less than systemic glucocorticoids. It is clear that the side effect of inhaled glucocorticoids is much less than systemic glucocorticoids. Moreover, the dose to produce the same anti-asthma potency is much less for inhalation therapy than in systemic therapy (See page 431, col. 1, second paragrpah). Therefore, in view of the teachings of Kelly and Hill and the state of the art at the time of filing, the systemic side effect is probably minimize. Even arguendo, the unexpected benefit are directed

towards the intended use, i.e., treating asthma, of the DHEA composition. Therefore, it is not even relevant to the teachings of the cited prior arts.

Applicant's arguments filed December 1, 2005 averring the unpredictability in the art, especially "in the insecticide field with homologs, isomers, and analogs of known effect insecticides have proven ineffective as insecticides" have been considered, but are not found persuasive. The citing of *In re Schechter* is misplaced. In the instant case, the cited prior arts teach the exact same compounds herein claimed. The cited prior arts do not teach the homologs, isomers, and analogs of DHEA or DHEAS. The only difference in prior arts teachings and that of the instant invention is the particle size recited. In view of the teachings of cited prior arts, one of ordinary skill in the art would have been motivated to optimize the particle size to the herein claimed particle sizes, absent evidence to the contrary.

Applicant's arguments with regards to the difficulties in achieving the inhalation formulations have been considered, but are not found persuasive. Examiner notes that the references are all published after the effective filing date of the instant application, which may or may not necessary reflect the state of the art at the time of the invention. The references provided merely point out the various factors that need to be considered when formulating aerosol formulations. The jet flow, propellants, various factors on device, solution or suspension are all well-known in the art that would affect the bioavailability and thereby the therapeutic efficacy of the inhalation formulation. Furthermore, in the Smyth references provided, it teaches different ways to improve the correlation of the *in vitro* and *in vivo* performance of inhalation. Therefore, there is

known in the art to optimize the delivery of active drugs through inhalation. Examiner notes that there is no evidence in the instant application as directed to the difficulties in developing particularly DHEA-S formulation, and how the applicant overcomes such difficulties. Even if the novelty or unexpected success lies in the specific inhalation formulation of DHEAS, there is no limitation recited to reflect such novelty in the pending claims. As discussed above, The only difference in prior arts teachings and that of the instant invention is the particle size recited. Therefore, possessing the teachings of the cited prior arts and the state of the art at the time of filing, one of ordinary skill in the art would have been motivated to employ inhalation route of administration for delivery DHEA-S.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Primary Examiner
Art Unit 1617